Lysosomotropic Agents in AIDS Treatment

TO THE EDITOR: There is currently considerable interest in the etiology, diagnosis and treatment of the acquired immunodeficiency syndrome (AIDS). While the incidence of AIDS continues to increase exponentially, there is no currently proved treatment or prophylactic agent.[1] Substantial evidence has accumulated to implicate a novel retrovirus—human immunodeficiency virus (HIV)—in the pathogenesis of AIDS. This virus appears to have a tropism for helper T lymphocytes expressing the T4 (CD4) antigen, and the cytopathic effect of the virus on helper T lymphocytes accounts for the major clinical manifestations of AIDS.[1] A recent report[2] suggested that the T4 antigen is in fact the cell surface receptor for the AIDS virus and that the virus subsequently enters the cell via endocytosis. The process of receptor-mediated endocytosis has been well characterized for a number of proteins, hormones, toxins and viruses, including retroviruses.[3-6] Acidification of the endosome is a frequent, if not universal, step in the endocytotic process.[3,4] It has been shown for a number of viruses (including retroviruses and human pathogens such as influenza A) that acidification triggers fusion of the viral membrane with the endosomal membrane, probably by a pH-induced conformational change in the viral membrane glycoprotein.[7] So-called lysosomotropic agents, weak bases which enter endosomes, have been shown to inhibit endosome acidification and thus block viral entry and infection[3,4,8-10] Two of these agents, chloroquine and amantadine, are widely used clinical drugs.

In the case of amantadine, although influenza A entry is blocked at clinically relevant concentrations, retrovirus entry is only inhibited at concentrations approximately two orders of magnitude higher. For chloroquine, clinically relevant plasma concentrations (100 to 300 ng per ml) are only three to ten times below the concentrations needed to cause 75% inhibition of viral entry in vitro.[8,11] Severe toxicity at higher doses precludes the use of substantially higher doses of chloroquine.[12] However, chloroquine is highly concentrated in certain tissues in vivo, notably in the cerebrospinal fluid (10 to 30 times plasma level), the reticuloendothelial system (6,000 times) and leukocytes (100 to 200 times).[13] This suggests that chloroquine could be effective in vivo, even though usual clinical plasma concentrations are somewhat below those needed for in vitro effects.

I suggest that amantadine, chloroquine and other antimalarials related to chloroquine[13-15] may be promising as rational agents for the prevention and early treatment of AIDS. Although their antiviral action of blocking pH-dependent viral entry into lymphocytes would be predicted to be a virustatic rather than virucidal action, they could still be of great potential value in preventing, slowing or arresting the relentless progress of the illness. Furthermore, the high concentrations attainable in cerebrospinal fluid suggest these agents might be especially valuable in treating central nervous system complications of AIDS where other drugs were excluded by the blood-brain barrier. Although evaluation of the anti-HIV effect of these drugs in vitro is a logical first step toward their clinical use, higher drug concentrations may be needed in vitro than in plasma due to the tissue concentrating effects described above. Since the effects of lysosomotropic agents can be additive in raising endosomal pH, the combination of these two drugs should be considered. Chloroquine has also been in wide use as a prophylactic antimalarial agent. Its relative lack of side effects, even during long-term administration, makes it a potentially attractive prophylactic agent for individuals known to be at high risk for AIDS. The low toxicity of these agents render them suitable as potential adjunctive treatments as well, in some form of combination chemotherapy.

I recommend that preclinical and clinical trials be carried out in research centers capable of measuring plasma drug levels, antibody titers and lymphocyte function in addition to clinical status so that a fair evaluation of the potential of these agents can be made.

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AIDS Vaccine Trial Volunteers Can Be Found

TO THE EDITOR: New California state legislation supportive of the development of an acquired immunodeficiency syndrome (AIDS) vaccine presumes that a sample of willing volunteers will submit to a vaccine trial. In terms of screening, subjects must be seronegative for the human immunodeficiency virus (HIV)—previously designated HTLV-III—at baseline, in a population where seroprevalence is increasing, and must be engaged in activity between baseline and follow-up likely to lead to viral infection. Injecting individuals with a vaccine, then expecting them to be engaged in behavior capable of exposure to HIV, poses ethical dilemmas. Testing persons for AIDS antibody before and after such a trial would require special assurances of confidentiality and may have psychological impact.[1] The question becomes, Who would volunteer?

Every six months since November 1983, the University of California, San Francisco, AIDS Behavioral Research

Project has gathered data on 676 San Francisco gay men's sexual practices and their willingness to take the AIDS antibody test.[2-4] In November 1985 we also surveyed respondents' willingness to participate in an AIDS vaccine trial. Of these respondents, 43% (292) reported that they would be willing to volunteer for such a trial, 14% (93) would not be willing and 43% (282) did not know whether they would volunteer. Only 22% (149) of the sample reported that they had been tested for antibodies to the AIDS virus, 72 of these persons reporting a negative status. There were 41 of these known antibody-negative persons who were willing to volunteer for a vaccine trial.

Vaccine trial volunteers were significantly more likely to have been tested for AIDS antibody (30%) than nonvolunteers (16%) or those who are unsure about volunteering (17%) ($\chi^2 = 16.2$, $df = 2$, $P = .00$). Nonvolunteers were more likely to have eliminated multiple-partner sexual activity capable of transmitting or receiving the AIDS virus (91%) than either volunteers (78%) or those unsure about volunteering (79%) ($\chi^2 = 8.0$, $df = 2$, $P = .02$).

Agreement with the following statements was surveyed of all respondents:

- I am concerned about the confidentiality of such a trial (88% agreed).
- I need to be reassured that the vaccine will not hurt me (92% agreed).
- Investigators should be sensitive to gay issues (97% agreed).
- I want to be paid to participate (19% agreed).
- I am willing to describe my sexual practices (95% agreed).
- I am likely to maintain the same type of sexual activity for the next year (93% agreed).
- I am likely to maintain the same number of sexual partners for the next year (89% agreed).
- I am willing to submit to antibody testing as part of this trial (77% agreed).
- I am willing to come to the University of California for the purpose of undergoing this trial (90% agreed).

Relationships between level of agreement with the above statements and overall willingness to volunteer were examined. One's decision to volunteer was related to being required to travel to the research site, reassurances about potential harm, desire for payment and willingness to take the antibody test. Concerns about confidentiality or about describing one's sexual practices did not relate to the decision for these men, who were already research participants. Those who expected to change their type of sexual practice were less likely to volunteer, and those who intended to reduce their number of sexual partners were more likely to say "no" or "I don't know" to the question of volunteering.

These results were drawn from a sample of highly cooperative gay men who have stayed with this study for several waves of data collection, thus they may not be representative of gay men in general. However, a sizable number of seronegative men from this group are willing to volunteer, given the proper assurances. More are willing whose antibody statuses have not yet been determined. A recruitment procedure could be devised that would find similarly cooperative men. Some amount of high-risk activity persisted in persons who were willing to volunteer for the trial in November 1985. The small overall percentage of the sample engaged in high-risk sex at that time (20%) reflects the successes in this city of public health education efforts. However, from the standpoint of vaccine trial screening criteria, more high-risk sex may need to be occurring in the test population. Also, given the high, stable seroprevalence of the AIDS virus in San Francisco,[5] other urban sites with lower AIDS virus seroprevalence may be better suited to a trial by the time investigators are ready to proceed.

The ethical issues associated with administering an untried vaccine to persons engaged in high-risk sex without discouraging this sexual activity are not addressed by this study. However, these results do suggest that problems in sampling for such a trial are not insurmountable, if the investigators are able to provide reassurances of safety and convenience to potential volunteers.

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Concept of Cognitive Versus Procedural

TO THE EDITOR: I have just read "Changing Physician Payment for Medicare Patients"[1] in the November issue.

It is time to call a halt to the spread of a practice that is inaccurate, misleading, divisive and insulting to a large part of the medical community. I refer to the attempt to divide physicians' services, or even the physicians themselves, into "cognitive" and "procedural."

If the elders of the American Society of Internal Medicine want to be reimbursed at a higher level, more power to them. But there is a reason why one consults a general surgeon to help evaluate atypical abdominal pain, or a vascular surgeon to unravel the causes of a swollen or painful leg. The repair of a thoracoabdominal aortic aneurysm or the relief of an intestinal obstruction due to metastatic colon cancer requires experience, knowledge, judgment and wisdom on the part of the surgeon.

More than ever, physicians need to hang together, or we shall most assuredly hang separately. Let's banish this "cognitive/procedural" malarkey from all respectable medical publications.

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